ABSTRACT BOOK

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THE FOUNDATION FOR GENDER-SPECIFIC MEDICINE

FONDAZIONE INTERNAZIONALE MENARINI

THE WORLD WRITES ON THE BODY:

HOW THE ENVIRONMENT IMPACTS THE PHENOTYPE

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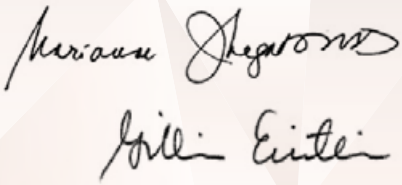
The 21st century began with the finalization of the description of the structure of the human genome, ushering in a profound change in our understanding what makes us what we are. We now have unprecedented power to understand the mechanisms and impact of genetic activity and the factors that modulate and control its expression. We are in the process of deciphering how age, hormones and the environment all modify behavior.

This symposium was constructed to set out the most exciting and significant science in the new field of epigenetics which is concerned with the factors that collaborate to modify genetic activity and thus mold the phenotype. Our expanding appreciation of the nature and complexity of epigenetics has produced a revolution in biomedical investigation and no less importantly, in how sociologists, anthropologists and psychologists among others consider the mechanisms of how experience changes behavior, susceptibility to disease and perhaps most importantly, how epigenetic modification of genetic activity is transmitted to future generations. Hopefully, the symposium will amplify the collaboration between biomedical investigators and social scientists by describing the final common pathway that explains how the environment modifies function.

Professors
Marianne J. Legato and Gillian Einstein
Presidents of the Meeting



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Abstract Book

Session I - The Intelligent Genome: What is the Molecular Mechanism of Adaptation?

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This ground-breaking symposium gathers together experts from two disparate groups of scientists: biomedical investigators working at the molecular level on gene physiology and social scientists investigating the impact of environmental experience on the human phenotype. Traditionally, discourse between the two groups has been limited and often contentious: the social scientist believed the impact on behavior of the milieu in which the individual exists was largely ignored by biomedical investigators. Biologists, on the other hand, were largely convinced that data from epidemiology, anthropology and other allied disciplines could not be quantified or predictive and largely ignored collaboration with sociologists. In fact, the delineation of the structure of the human genome at the beginning of this century afforded scientists with opportunities to explore the factors that modify gene expression in ways that had never before been possible. The consequences of this paradigm-shifting discovery has changed our view of the primacy of Darwin's description of evolution as a consequence of random genetic mutation. With logarithmically increasing competence we are able to exercise deliberate, focused and precise genetic manipulation. It is now clear that experience impacts genetic expression and moreover that that impact can be and in fact, often is transmitted to progeny. This symposium focuses on the new and ever more detailed and precise view of the molecular mechanisms set in motion by experience, which triggers adaptive patterns of genetic expression. The material presented here is an important initial step in resolving the classic divide between experts about the relative importance and the link between nature and nurture in producing the phenotype. Thus, we are addressing questions which have never before

had answers and in do doing, changing our view of what makes us ourselves and how we adapt to survive in a changing environment.

Key words: nature, nurture, gene expression

References:

1. Legato M. J. (ed). Principles of Gender-Specific Medicine. Third Edition. Gender in the Genomic Era. Elsevier. 2017
2. McCarthy M. M. and Arnold A: Nature Neuroscience 2011. 14(6).677-683.
3. Keverne E. B. and Curley JP. Neuroendocrinology. 2008.29:398-412.
4. Saletore Y. et al. Genomebiology. 2012.13:175.
5. Conley D. Biodemography and Social Biology. 2009.55:238-251

Session I - The world writes on the body: Does the experience of gender contribute to sex differences?

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Epigenetics is a powerful explanatory mechanism for how experience and environment can shape biology - in explaining how experience gets under our skin or, the world writes on our bodies. Scientists have turned their attention to how a range of life experiences - nutrition, neurotransmitters, aging, early life adversity, mothering, stress, pre- and post-natal environment, and socioeconomic status - all effecting our gene expression - alter our health and our behaviour. Sex and gender influence our biologies as well. Sex refers to the biological factors resulting from sex chromosome compliment, either XX or XY. It includes genes, the expression of other chromosomes, sex hormones, physiology and anatomy. Gender is a more complex, multidimensional socio-cultural construct with multiple components including gender roles, gender identity, gender relations and institutionalized gender. Sex and gender influence all health domains, from basic disease mechanisms and efficacy of treatment, to health service utilization and the uptake of health-related interventions. Gender, as a social structure that is continuously achieved through interactions with the world, may have important implications for epigenetic changes throughout life and yet, with the exception of epigenetics and sexual differentiation as well as of mothering, these are notably missing from studies of epigenetic markers. When sex differences are studied in rodents, important findings result. Indeed, the epigenome has been identified as a driver of sexual differentiation with experimentally induced transient reduction in the levels of the DNA methyl-CpG-binding protein 2 (MeCP2) during the sensitive period for sexual differentiation permanently reducing the expression of vasopressin in the amygdala of males compared to those of females, eliminating well established amygdala sex differences. Epigenetic regulation of enzymes

responsible for the synthesis and breakdown of steroid hormones, as well as the regulation of steroid hormone receptors have been shown to drive sex differences in juvenile play and sexual behaviour in rodents as well as the development of sex differences in the anatomical structure of regions known to be sexually dimorphic also in rodents, such as the Medial Preoptic Area. What is less well studied are sex differences in human epigenetic regulation and the influence of the gendered world on epigenetic changes. For example, ground breaking work on the epigenetic regulation of the glucocorticoid receptor in children with childhood abuse was unfortunately only studied in men. One example of gender inducing changes might be 'women's work' which is often characterized by high emotional work requirements. These professions are associated with higher levels of ill health, burnout, emotional exhaustion, anxiety and depression. An exploration of physiological stress responses across various socially structured gendered work organizations, may actually help re-frame so-called biologically determined sex differences to sex differences induced by the gendered world. In this talk we will discuss epigenetic studies that consider sex as well as gender highlighting the importance of including these in any study of how epigenetic changes modify our biologies.

References:

1. Hertzman C. & Boyce T. (2010) How Experience Gets Under the Skin to Create Gradients in Developmental Health. Annual Review of Public Health, 31. Institute of Gender and Health, Canadian Institutes of Health Research. Online Training Modules: Integrating sex and gender in health research. http://www.cihr-irsc.gc.ca/e/49347.html

2. McCarthy, M. M., Nugent, B. M., & Lenz, K. M. (2017). Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain. Nature Reviews Neuroscience,18(8), 471.

3. Einstein, G. & Shildrick, M. (2009). The postconventional body: Re-theorizing women's health. Soc. Sci. Med. 69: 293.

Session II - Gene-environment interplay in behaviour

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Previous ideas about the origins of our individual differences were based around the nature-nurture dichotomy. Current research shows that not only do we bring genetic predispositions along with us when we are born but our genes also listen to our experience as we develop. The new field of social epigenetics investigates how our behaviour and physiology responds to our experience through changes in the way genes express themselves during development and under certain environments. This gene-environment interplay acting throughout development moulds our bodies and minds-making us who we are.

Session II - Dopamine and Epigenetics

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A dysfunctional dopamine transmission have been causally linked to cognitive and functional impairments proper of a number of neuropsychiatric disorders, such as schizophrenia (SZ). Indeed, the dopamine hypothesis of schizophrenia is one of the most credited hypotheses for the genesis of this disorder, based on the therapeutic benefits of dopamine antagonists in patients and imaging results. Dopamine levels in the brain are strictly regulated by convergent signaling from different neurotransmitters as well as by proteins involved in the presynaptic control of this function on dopaminergic neurons. The dopamine D2 receptor (D2R) is one of them; D2R is responsible for inhibiting the synthesis and release of DA from dopaminergic neurons, acting as an autoreceptor. We generated site-specific knockout mice lacking D2R selectively from dopamine (DA) neurons (hereafter referred as DA-D2RKO) to analyze, in vivo, the consequences of D2 autoreceptor deficiency. DA-D2RKO mice present a "psychotic" behavior characterized by prefrontal cortex (PFC) deficits and striatal hyperactivity. Molecular analyses in the adult DA-D2RKO mice showed the presence of a PFC-specific epigenetic reprogramming of gene expression. Interestingly, the reprogramming of PFC neurons involves the repression of gene expression caused by an increase of epigenetic repressive mark on histone H3. Also relevant to SZ, we found that these modifications appear during adolescence. The analysis of the molecular mechanisms underlying the dopamine induced epigenetic modifications will shed light on the role of dopamine signaling in the cortex during development and in the adult and promise to generate important information on neuropsychiatric disorders like SZ, which might arise from mechanisms linked to dysfunctional neurotransmission.

Session III - Epigenetics, nutrition and the circadian clock

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The circadian clock controls a remarkable array of physiological and metabolic functions.
As disruption of the circadian clock may lead to metabolic disorders including cancer (**1**), it is essential to understand how circadian rhythms and metabolic processes interact on a cell and tissue-specific level. Accumulating evidence indicates that clock-driven regulation of metabolism utilizes a variety of cellular pathways. This control is exerted in large part at the transcriptional level on thousands genes expressed in a cyclic manner. The highly specialized transcriptional machinery governing clock functions is organized in feedback autoregulatory loops and controls a significant portion of the genome. These oscillations in gene expression are associated with critical events of chromatin remodeling that provide plasticity to circadian regulation. We have unraveled the molecular pathways implicated in the epigenetic control by the circadian clock, including the discovery of the unexpected acetyltransferase activity of the protein CLOCK, the implication of the SIRTs deacetylases and the essential role played by the H3K3 tri-methyltransferase MLL1.
Moreover, these molecular pathways establish several intimate links with metabolic pathways, such as the cyclic utilization of NAD+ by SIRT1 and the intimate relationship with the aging process (**2**). Finally, these molecular mechanisms insure the flexibility of the circadian clock and its capacity to be reprogrammed by nutritional challenges (**3**). Our findings stress the role of the circadian clock in linking epigenetics, enzymatic control and cellular metabolism. This research has far-reaching implications for human physiology and disease.

References:

1. Masri S., Papagiannakopoulos T., Kinouchi K., Liu Y., Cervantes M., Baldi P., Jacks T., Sassone-Corsi P. (2016) Lung adenocarcinoma distally rewires hepatic circadian homeostasis.
2. Sato S., Solanas G., Peixoto F. O., Bee L., Symeonidi A., Schmidt M. S., Brenner C., Masri S., Benitah S. A., Sassone-Corsi P. (2017) Circadian reprogramming in the liver identifies metabolic pathways of aging.
3. Eckel-Mahan K. L., Patel V. R., de Mateo S., Orozco-Solis R., Ceglia N. J., Sahar S., Dilag-Penilla S. A., Dyar K. A., Baldi P. and Sassone-Corsi P. (2013) Reprogramming of the circadian clock by nutritional challenge.

Session III - Genomic imprinting: regulation, roles and environmental influences

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The expression of genetic information is controlled in part by the way genes and their associated proteins are structured and modified in specific cell lineages and tissues. Such 'epigenetic regulation' plays essential roles in development, health and well-being and is influenced by the environment (Feil & Fraga, 2012). One of the best-studied epigenetic phenomena in mammals is genomic imprinting, which controls hundreds of developmental, metabolic and behavioural genes in mammals such that these are expressed from one of the two parental copies only (Peters, J. 2014). Some imprinted genes are expressed from their maternal (oocyte-inherited) copy only; others are expressed from the paternal (sperm-inherited) copy only. Imprinted genes are clustered in large conserved domains that map to specific chromosomes. Each imprinted domain is controlled by a master regulatory element, and these are often referred to as 'imprinting control regions' (ICRs). ICRs are marked by repressive DNA methylation in either the sperm or the oocyte. After fertilisation, these DNA methylation marks are somatically maintained all the way through to adulthood, and it is these 'epigenetic imprints' that control the unusual mono-allelic expression of imprinted genes.

Despite their importance, it remains poorly understood how the DNA methylation imprints at ICRs are maintained throughout development (Kelsey & Feil, 2013). In humans, early embryonic perturbations in the maintenance of methylation imprints are causally involved in many different congenital diseases (Girardot et al. 2013). Various toxic and dietary components can readily perturb the establishment and/or maintenance of DNA methylation

imprints (and hence, imprinted gene expression) as well. Also different aspects of assisted reproduction are thought to stochastically affect genomic imprinting. In the presentation, I will introduce the importance of genomic imprinting. I will discuss with the audience selected examples of how environmental cues perturb imprinting and related other epigenetic repression mechanisms (Pathak and Feil, 2018) and that this can have long-lasting phenotypic consequences.

References:

1. Feil R & Fraga MF (2012). Epigenetics and the environment: emerging patterns and implications. *Nature Rev Genet* 13, 97-109.

2. Kelsey G & Feil R (2013). New insights into the establishment and maintenance of DNA methylation imprints in mammals. *Phil. Trans. R. Soc.* B, 368, 20110336.

3. Girardot M, Feil R & Lleres D (2013). Epigenetic deregulation of genomic imprinting in humans: causal mechanisms and clinical implications. *Epigenomics* 5, 715-728.

4. Peters J (2014). The role of genomic imprinting in biology and disease: an expanding view. *Nature Rev Genet* 15, 517-530.

5. Pathak R & Feil R (2018). Environmental effects on chromatin repression at imprinted genes and endogenous retroviruses. *Current Opinion in Chemical Biology*, in the press.

Session III - Epigenetic changes during lifetime: the effect of environment

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It is well-known that genetic and environmental factors interact to determine phenotype, although the underlying molecular mechanisms are still poorly understood. There is growing evidence that the effect of environmental cues is mediated, at least in part, by epigenetic modifications, but the role of factors such as the target tissue and the developmental stage is still under debate. In my talk, I will show how the epigenome changes during lifetime, and how lifestyle choices can modulate the process, paying special attention to bad dietary and other habits and the stress that we are subject to on a daily basis. These epigenetic changes can affect the homeostasis of our cells and tissues, possibly playing a role in the development of disease. I will also present recent data about changes of interindividual variability during lifetime which suggest that the effect of environmental factors is highly dependent on the developmental stage involved.

Session IV - Psychobiological Consequences of Child Maltreatment

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Adversity in early life, such as childhood abuse, neglect and loss, is a well-established major risk factor for developing a range of psychiatric and medical disorders later in life. Biological embedding of maltreatment during development is thought to underlie this long-term increased risk. Our results suggest that childhood trauma in humans is associated with sensitization of the stress response, glucocorticoid resistance, decreased oxytocin activity, inflammation, reduced hippocampal volume and changes in cortical fields that are implicated in the perception or processing of the abuse. The consequences of childhood trauma are moderated by genetic factors and mediated by epigenetic changes in genes relevant for stress regulation. Understanding longitudinal trajectories of biological embedding, and their moderation by gene-environment interaction, is critical to enable us to design novel interventions that directly reverse these processes and to derive biomarkers that identify children who are at risk to develop disorders or are susceptible to a specific intervention.

Session IV - Using Gene-Environment Interactions to Interrogate the Impact of the Social Environment on Smoking Behavior

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The recent availability of molecular genetic data in large population-representative studies has made it possible to examine the interplay between whole-genome measures of genetic risk and the social environment in ways that were previously only possible in twin or family studies. Research on gene-environment (G x E) interactions—broadly defined as any situation where individual response to environmental risk differs by genotype—has shown genetic risk is amplified, or reduced, in the presence of a particular environment; similarly, the effects of the environment are influenced by the presence or absence of specific genetic susceptibilities (Rutter, 2006). The feedback between "G" and "E" provides social researchers with another lens for understanding how aspects of the social environment may contribute to disparities in health and education across the life course (Schmitz & Conley, 2017). This talk will present recent work that used the Vietnam-era draft lottery and polygenic scores (PGSs) to assess whether genetic susceptibility to smoking is influenced by risky environments in young adulthood (Schmitz & Conley, 2015). Specifically, using data from the Health and Retirement Study (HRS), we interact a PGS for smoking initiation with instrumented veteran status in an instrumental variables (IV) framework to test for genetic moderation (i.e. heterogeneous treatment effects) of veteran status on smoking behavior and smoking-related morbidities. We find evidence that veterans with a high genetic predisposition for smoking were more likely to have been smokers, smoke heavily, and were at a higher risk of being diagnosed with cancer or hypertension at older ages. In addition, smoking behavior was significantly attenuated

for highrisk veterans who attended college after the war, indicating post-service schooling gains from veterans' use of the GI Bill may have reduced tobacco consumption in adulthood.

References:

1. Rutter M. (2006). Genes and behavior: Nature-nurture interplay explained. Malden, MA: Blackwell.
2. Schmitz L. L., & Conley D. (2015). The long-term effects of Vietnam-Era conscription and genotype on smoking behavior and health. *Behavior Genetics*, 46(1): 43-58.
3. Schmitz, L. L., & Conley D. (2017). Modeling gene-environment interactions with quasinatural experiments. *Journal of Personality*, 85(1): 10-21.

Session IV - Opportunities for prevention & intervention in child protection services: lessons from Canada

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Infancy and early childhood are critical periods of development for children which lay the foundation for future learning, behaviour and physical and mental health concerns. During this time of great opportunity, children are also particularly vulnerable to negative experiences such as inappropriate or abusive parenting, a lack of nurturing and unpredictable or chaotic environments. A greater understanding of how the child welfare system responds to these children is critical to informing appropriate research, practice, and policy efforts to promote the well-being of children.

This presentation will discuss findings from the Ontario Incidence Study of Reported Child Abuse and Neglect-2013 (OIS-2013) with a particular focus on infants and young children. The OIS-2013 is the fifth provincial study to examine the characteristics of children and families identified to the Ontario child welfare system. A profile of young children and their caregivers will be outlined along with current service provision patterns. The findings of our analyses underscore the particular vulnerability of children identified to child welfare and the necessity of working in partnership with other sectors and multiple disciplines for effective intervention and prevention efforts.

Through the OIS, key clinical factors in the decision to provide ongoing services have been identified. Child welfare professionals can strengthen and support existing caregiver-child relationships through informed practice though an assessment of the strengths and needs of children and families.

References:

1. Fallon B., Trocmé N., Filippelli J., Black T., & Joh-Carnella N. (2017). Responding to safety concerns and chronic needs: Trends over time. *Child and Adolescent Psychiatry and Mental Health*, 11(60). doi:10.1186/s13034-017-0200-5
2. Fallon B., Filippelli J., Black T., Trocmé N., & Esposito T. (2017). How can data drive policy and practice in child welfare? Making the link in Canada. I*nternational Journal of Environmental Research and Public Health*, 17(1223). doi:10.3390/ijerph14101223
3. Fallon B., Chabot M., Fluke J., Blackstock C., Sinha V., Allan K., & MacLaurin B. (2015). Exploring alternate specifications to explain agency-level effects in placement decisions regarding aboriginal children: Further analysis of the Canadian Incidence Study of Reported Child Abuse and Neglect Part C. *Child Abuse and Neglect*. Advanced Online publication. doi:10.1016/j.chiabu.2015.04.012

Session V - Mothering begets mothering across generations: Effects of early experience

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What makes a mother want to mother? In most mammalian species, the female is not normally maternal until she herself gives birth. However, at the end of pregnancy and at birth the hormonal and neurochemical changes that occur result in a shift in the mother's emotional state, her attraction to young, and her attention to them. Among humans as well, mothering motivation tends to increase after birth and is affected by a shift in mothers' appraisal of babies, an enhanced emotional sensitivity and lability and a change in a number of executive (cognitive) functions. The present talk will first discuss the phenomenology of mothering in selected mammals (rat and human) and the role of hypothalamic, limbic, and cortical system function in its regulation. It will then describe studies which show that variations in mothering behavior affect the brains of their daughters and, in doing so, affects their subsequent maternal and associated behaviors.

Animal (rat) studies show that early separation from mother and siblings through artificial rearing (AR) results in offspring that **1**) at birth show reduced apoptosis and evidence of neuronal function in the maternal neural circuit, and grow up, showing **2**) less intense maternal behavior, **3**) altered patterns of hedonic, emotional, and cognitive, function and **4**) reduced levels of accumbens extracellular DA release in response to pup stimulation. Licking-like 'replacement' stimulation during early life reverses many of these effects. Longitudinal correlational human studies show that retrospectively reported early adversity in family of origin (neglect/abuse) is associated with **1**) reduced maternal sensitivity,

2) elevated levels of depression and anxiety and **3**) non-normative BOLD activation patterns to infant- as opposed to -noninfant stimuli in many of the same limbic and cortical sites.

Taken together these studies suggest that in both animal models and in humans, early life experiences of the mother affect the intensity and/or quality of her maternal behavior and, hence, the development of maternal and emotional function in the next generation.

Session V - Epigenetic programming by maternal behavior

Moshe Szyf
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Early life exposures are known to have long-lasting impact on the phenotype later in life. What are the mechanisms that mediate between exposure and long-term effects on physical and mental health? DNA methylation is a "chemical" mark on DNA that provides the "software" that is programming our DNA during the building of our tissues and organs throughout early development. We hypothesize that epigenetic processes such as DNA methylation also program our DNA in response to early life experience. Thus, DNA methylation confers an "experiential identity" upon our DNA.

We will review data from rodents, nonhuman primates and humans that is consistent with the idea that differences in "maternal care" result in system wide changes in DNA methylation that are detectable later in life in the offspring. Experiments in rodents demonstrated that low maternal care resulted in changes in DNA methylation in the glucocorticoid receptor gene in the hippocampus, which remained throughout life and altered the life-long behavior of the offspring increasing anxiety and responsivity to stress. Similarly, in humans we noted differences in DNA methylation in the glucocorticoid gene in hippocampi of adults who were abused as children. Our later studies show that these changes in DNA methylation in response to early adversity affected broad regions of the genome and that they are not limited to the brain and occur in the immune system as well. We will present data from nonhuman primates indicating that overlapping genes are altered in response to postnatal maternal deprivation in the

immune system and the prefrontal cortex. Early life maternal deprivation alters the normal trajectory of the evolving DNA methylation during development in a sex specific manner(**1**). In rhesus macaque maternal social status defines DNA methylation profiles in the placentae at birth suggesting that social positioning defines DNA methylation profiles even before the offspring experiences social contacts(**2**). We have evidence from a study of a natural disaster in humans, the Quebec ice storm of 1998, that maternal objective stress is associated with changes in DNA methylation in children that are detectable in T cells and remain into adolescence. This provides evidence in humans for a causal link between maternal stress and offspring epigenome. We propose that the changes in DNA methylation in response to early life experience are "adaptive genomic" mechanisms that adapt life-long genome programming to the anticipated life-long environment based on stress signals received during gestation and early life. What is the mechanism that mediates between maternal stress and offspring epigenome? We will discuss the hypothesis that stress hormones might be mediating the genome wide and system wide response of the methylome to stress. Glucocorticoids might act as "integrators" that translate the social stress signals during gestation to genome wide methylation changes across multiple systems.

The idea that DNA methylation is mediating the effects of early exposures on later phenotypes has important implications for mental health. DNA methylation biomarkers could be used to screen for past exposures, to predict high risk for developing pathology later in life. Epigenetic marks are potentially reversible and therefore epigenetically mediated phenotypes could potentially be reprogrammed by epigenetic therapeutics(**3**). Examples of reversing experience triggered phenotypes such as cocaine addiction through an epigenetic approach will be discussed.

References:

1. Massart R, et al., The Signature of Maternal Social Rank in Placenta Deoxyribonucleic Acid
   Methylation Profiles in Rhesus Monkeys. Child Dev. 2017 May;88(3):900-918. PMID: 27739069.
2. Szyf M. Prospects for Medications to Reverse Causative Epigenetic Processes in
   Neuropsychiatry Disorders. Neuropsychopharmacology. 2017 Jan;42(1):367-368. PMID: 27909326;
3. Massart et al., Early life adversity alters normal sex-dependent developmental dynamics of DNA methylation. Dev Psychopathol. 2016 Nov;28(4pt2):1259-1272. PMID: 27687908.

Session V - The developmental origin of health and disease: a sex and gender perspective

Annie Duchesne
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In the last three decades, the Development Origins of Health and Disease hypothesis generated a wealth of research redefining our understanding of how the environment shapes health trajectories. This research shows that individual differences modulate the relationship between environment and one's health. In particular, accumulating evidence demonstrates differential effects of prenatal maternal stress (PNMS) on men and women's health. To date, it remains unclear what factors contribute to those differences. Importantly, while both biological sex and sociocultural gendered variables have been considered, the latter is often overlooked. By adopting a sex and gender perspective, this presentation aims at providing new avenues for understanding how the environment, in particular prenatal maternal stress, can differently impact the health of individuals throughout the life span. The presentation will first focus on a recent study conducted within the Project Ice Storm investigating the relation between PNMS and pubertal timing. Early pubertal onset results in both physical and mental health risks, an effect particularly observed in girls. Findings from this study revealed that daughters of mothers who experienced greater PNMS had earlier pubertal timing, an association that was mediated through increased body mass index during childhood. Secondly, I will explore how gender contribute to the health-related risks observed in early maturing girls and the consequences gender may have on the differential effects of PNMS on the mental health of both men and women. I will conclude this presentation by discussing more broadly how the adoption of a sex and gender perspective may improve our understanding of the Developmental Origins of Health and Disease.

Session VI - Intergenerational transmission of socioeconomic disadvantage: What are the biological mechanisms?

Martha J. Farah
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Socioeconomic status (SES) predicts a wide variety of important life outcomes, from physical and mental health to cognitive ability. Given that SES tends to be stable across generations, this means that people born to poor families are disadvantaged from childhood on in terms of their future SES, capabilities and health. Why does poverty persist across generations? What mechanisms are responsible for the "cycle of poverty?"

In my talk I will attempt to lay out a number of possibilities, some of which involve epigenetic mechanisms. But before beginning, a few provisos: First, the possibilities reviewed here are not mutually exclusive; we should not look for the single right answer. It is likely that many different mechanisms are involved in linking low SES childhoods to their adult correlates, with many-to-many relations between aspects of childhood environment and aspects of life outcomes. Second, the evidence base is still sparse and hypotheses are woefully underdetermined by the available data. Human studies are generally observational and uncontrolled and animal studies are limited by the obvious fact that animals do not have SES! Third, although childhood poverty and maltreatment are somewhat correlated, they have distinct effects yet are often lumped together as early life adversity. Despite these challenges, progress is being made, thanks to growing interest in the neuroscience of SES and powerful new methods to study SES at the molecular, neural and behavioral levels.

The literature to be reviewed in my talk will review the following pathways from SES to brain and behavior. The myriad effects of stress on the brain, as demonstrated by research with humans and animals, suggests an

important role for stress in socioeconomic disparities in health, conveyed primarily though neural mechanisms. While this might not be surprising in connection with mental health, it is also true for physical health via the brain's transduction of stress into inflammation and other immune processes. There is also evidence that stress physiology plays a role in cognitive ability and socioeconomic disparities in cognition.

Parental behavior is another another pathway through which low SES impacts child development, as stress affects parents. In addition, culturally based differences in parenting goals and practices constitute yet another possible pathway, also to be reviewed in my presentation.

More tangible causes in the physical world, including toxins and nutrition, are also likely to be responsible for lifelong SES disparities in health and capabilities. And we know that these factors often synergize with the psychological factors outlined above.

Finally, prenatal life lays the foundation for brain development, and prenatal differences linked to maternal SES are well-established. SES effects on brain development are apparent early in life (eg, differences in grey matter volume at 5 weeks) and prenatal causes are likely given SES-linked epigenetic changes in the child and inflammatory processes that predict early life brain growth.
I will conclude with open questions, including gender differences in the effects of poverty on the brain, and priorities for future research.

References:

1. Farah M. J. (2017). The neuroscience of socioeconomic status: Correlates, causes, and consequences. *Neuron, 96*(1), 56-71.

2. Swartz J.R., Hariri A.R., and Williamson D.E. (2017). An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents. Mol. Psychiatry 22, 209–214.

Session VI - SmallRNAs transmit big epigenetic message: Intergenerational reprogramming of metabolism

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We have established a Drosophila model of intergenerational metabolic response (IGMR), and found that feeding male flies a high-sugar diet two days before mating modulates the expression of metabolic and epigenetic genes in the embryo, and ultimately the triglyceride storage in the adult fly. We are now investigating the molecular mechanisms of IGMR in greater detail and our preliminary data suggests that piwi and possible piwi-associated smallRNAs in sperm are important in transmitting paternal dietary information to offspring epigenetic memories. Together, these data begin to outline a mechanistic framework for a regulatory system that generates phenotypic diversity under normal conditions, and critically, that mediates intergenerational metabolic responses to paternal nutrition.

Session VI - The Impact of Maternal Psychosocial Stress on the Fetus and its Future life

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The "The World Writes On the Body", the title of this Congress emphasizes the impact of the environment on our phenotype. It is of utmost important to understand that this environment is not only the world in which we live but perhaps and even more so the environment in which we develop as fetuses (**1**). The concept of "Developmental Origins of Health and Disease" or " Fetal Programming" is profoundly changing our perception of the effect of the intrauterine environment on our life. Indeed, the intrauterine environment is currently regarded by many as the probable most important phase in our life where future health and disease are determined to a large extent. We realize now that one genotype may lead to different phenotypes. The intrauterine reality relates closely to the external reality, thus whatever is affecting the pregnant woman may reach her unborn child leading to epigenetic modifications of its genome. The affects of the intrauterine environment are not restricted to the somatic development of the fetus but may also have an impact on the mental development in its the future life. It has been shown that the offspring of pregnant women who have experienced unusual stress situations, such as in the course of nature related or man-made disasters and war will be at a higher risk for mental disturbances and disease later in their lives. There is a large amount of data available from animal and human studies, which shows the log-lasting detrimental effects of maternal stress on offspring, both, somatically as well as mentally. Maternal stress has been associated with various adverse effects in the offspring such as preterm birth (**2**), congenital heart defects (**3**), obesity (**4**) , asthma (**5**) impairment in cognitive function (**6**) , child development delay (**7**) and impaired mental health (**8**). Finally, maternal

stress may also result in a reduction of telomere length in the offspring, which in turn has been implicated in the reduction of longevity (**9**). All of these should be a cause of concern for society and for health care regulators and may raise the need for re-modelling health care infrastructures related to the treatment of pregnant women.

References:

1. Glezerman M. In: Legato M. J. (ed): Principles of Gender-Specific Medicine. Academic Press 2017,

2. Lilliecreutz et al. BMC Pregnancy and Childbirth . 2016; 16:5

3. Zhu J. L., et al. Pediatrics. 2013;131(4):e1225-30

4. Hohwu L. et al. PLoS One. 2014;9(5):e97490

5. Douros K. et al Front Pediatr. 2017 , 20;5:202.

6. Behrman R. E. and Stith Butler A., (eds). IOM. The National Academies Press, 2006.

7. Mughal M. K. et al l J Affect Disord. 2018; ;234:318-32

8. Van den Bergh B. R. H. et al.Neurosci Biobehav Rev. 2017, Jul 28

9. Entringer et al, AJOG. 2013,208 134.

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Session VII - Using olfaction to study intergenerational imprints of stress

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Stressors experienced by parental environments can influence future generations. One of the most discussed examples of such intergenerational influences of stress comes from the observation that exposure of pregnant women to the Hunger Winter of 1944 profoundly affected the physiology and behavior of the gestating babies and subsequent generations. Needed to understand the mechanisms of such intergenerational influences of stress are protocols wherein a parental generation is subjected to perturbations that can then be followed across generations. Toward this goal, we use structural, functional and genetic properties of the olfactory system to follow imprints of stress across generations. More specifically, we expose F0 mice to an olfactory fear conditioning protocol wherein an odor is paired with a mild foot-shock. This allows us to ask how the quality of an environmental cue associated with an aversive outcome in the parental generation (F0) is perceived and inherited by future offspring (F1 and F2 generations). We found that fear conditioning adult mice (F0 generation) to Acetophenone causes subsequently conceived F1 and F2 male offspring to display a behavioral sensitivity to Acetophenone, despite their having no prior exposure to this odor. Acetophenone is detected by the M71 odorant receptor in the Main Olfactory Epithelium and we find that the F1 and F2 generations have increased numbers of M71 neurons in the nose, and larger M71 glomeruli in the olfactory bulbs indicative of structural changes in the nervous system accompanying the behavioral sensitivity. Cross-fostering experiments and IVF experiments suggest that the intergenerational effects

of parental olfactory experience are inherited at the level of behavior and structure These data lead us to conclude that pre-conception parental olfactory experience can profoundly influence how future generations navigate their environments as adults. From a translational perspective, this work allows us to appreciate how parental experiences may influence the nervous systems of future generations potentially contributing to inherited risk for the manifestation of neuropsychiatric disorders such as phobias, anxiety, and Post Traumatic Stress Disorder (PTSD). In my talk, I will use this framework provided by olfaction to communicate our efforts to prevent intergenerational influences of stress from perpetuating across generations and some mechanistic insights into this phenomenon.

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Session VII - Epigenetics of Cardiovascular Disease: "Peeling the Onion" to Identify the Missing Link between Gene-Environment Interaction and Disease Expression.

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Cardiovascular Disease (CVD), as a whole, is projected to cost the United States of America roughly US$400 billion a year before the end of this decade - that is 1.5 in every 6 health care dollars. Not surprisingly, this amount exceeds costs of any other disease group and similar trends and impact are observed globally. Furthermore, CVD burden is expected to worsen due to an aging population and a shift in environmental risk factors toward diets with higher sodium, carbohydrate and fat content, as well as sedentary lifestyles.

While genome-wide association studies (GWAS) have become useful tools in the identification of disease-associated genetic variants, conventional views do not sufficiently explain the well-known link between CVD and environmental influence. We propound that epigenetics, defined as chromatin-based mechanisms cardinal in the regulation of gene expression that do not involve changes in the DNA sequence per se, represents the missing link. Moreover, epigenetics provides a molecular basis for understanding how the environment impacts the genome to modify cardiovascular disease risk over the lifetime of a cell - and its offspring. The nuclear-based mechanisms that contribute to epigenetic gene regulation can be broadly separated into three unique - but highly interrelated - processes: (**1**) DNA methylation and hydroxymethylation; (**2**) histone density and post-translational modifications; and (**3**) RNA-based mechanisms. Together they complement the cis/trans perspective on transcriptional control paradigms in cardiovascular system. This presentation aims to provide an intuitive view of the interplay between epigenetic function and CVD, with a focus on cell biology and continuous phenotypic refinement. Additionally, we highlight

emerging concepts on transgenerational epigenetic inheritance and on epigenetic gene regulation - highly relevant to atherosclerotic cardiovascular disease.

Epigenetics continues to advance as an element of paramount importance in the characterization of CVD. Its integration with the evolving knowledge on phenotypic clustering may well be considered as one of the pillars of precision cardiovascular medicine - geared towards a more personalized approach to patient care away from the "one size fits all" approach for disease prevention, diagnosis, and management.

References:

1. Benjamin E. J., Virani S. S., Callaway C. W., et al. Heart Disease and Stroke Statistics - 2018 Update: A Report from the American Heart Association. Circulation. 2018; CIR.0000000000000558.

2. Peden J. F., Farrall M. Thirty-five Common Variants for Coronary Artery Disease: The Fruits of Much Collaborative Labour. Human molecular genetics. 2011 Oct 15; 20(R2):R198 - 205

3. Whitelaw N. C., Whitelaw E. Transgenerational Epigenetic Inheritance in Health and Disease. Current opinion in genetics & development. 2008 Jun; 18(3):273 - 9

Session VII - Sex/Gender Correlates of Glucocorticoid Functioning and Allostatic Load

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Every cell is sexed, every person is gendered, and every organism is stressed. Whereas sex refers to a multi-dimensional construct that includes genes, anatomy, gonads, and hormones that collectively define us as male or female, gender refers to an array of socio-culturally constructed roles, orientations, and identities that further influence within-sex variations in stress and coping. Diverse sexual orientations and gender identities are also related to unique sets of exposures and experiences that correspond with health inequalities that are the focus of my current postdoctoral research. In this talk, I will share my transdisciplinary research program that nuances sex, gender, and sexual identity in relation to stress biology and mental health. By applying a sex- and gender-based analysis that appreciates individual variation beyond sex binaries, I will demonstrate how one's sex, sex hormones, gender-roles, and sexual identity uniquely influence functioning of the stress hormone cortisol and multi-systemic physiological dysregulation known as allostatic load linked to physical and mental health. The take-home message of this decade's worth of integrative neuroscience research can be summarized as follows: when studying stress-related phenomena that appears to differ between the sexes, accounting for both biological factors like sex hormones and gender-based factors like gender-roles and sexual orientation allows researchers to delineate inter-individual diversity more fully. This approach provides a powerful framework to help solve health problems that cannot be easily explained by focusing solely on binary sex differences.

References:

1. Juster R. P., McEwen B. S., & Lupien S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, 35(1), 2–16.

2. Juster R. P., Hatzenbuehler M. L., Mendrek A., Pfaus J. G., Smith N. G., Johnson P. J., et al. (2015). Sexual orientation modulates endocrine stress reactivity. *Biological Psychiatry*, 77(7), 668–676.

3. Juster R. P., Pruessner J. C., Desrochers A. B., Bourdon O., Durand N., Wan N., et al. (2016). Sex and Gender Roles in Relation to Mental Health and Allostatic Load. *Psychosomatic Medicine*, 78(7), 788–804.

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